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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/726,211	10/04/96	TORMO M	UTXC:504

HM11/0707

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EXAMINER	
SCHWARTZMAN,R	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/07/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/726,211	Applicant(s) Tormo et al.
	Examiner Robert Schwartzman	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Jun 15, 1998* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-37* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

This Office action is in response to the amendment filed June 15, 1998. New claims 21-37 have been added. Claims 1-37 are pending in the application.

Claim Rejections - 35 USC § 112

All rejections made in the previous Office action under 35 U.S.C. 112, first and second paragraphs have been withdrawn in view of the amendments to the claims and applicants' arguments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is vague and indefinite as it recites "oligonucleotide nucleotide" in line 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green et al. in view of Tari et al. This rejection is maintained for the reasons of record in the previous Office action mailed March 16, 1998.

To summarize the rejection, Evan, Reed and Green et al. each teach antisense oligonucleotides targeted to Bcl-2. The oligonucleotide preferably is targeted to the translation initiation site of Bcl-2. The antisense oligonucleotide or an expression construct encoding the antisense oligonucleotide can be delivered into a cell as a liposome composition. Evan, Reed and Green et al. do not teach liposomes composed of neutral phospholipids. Tari et al. teaches compositions comprising an antisense oligonucleotide encapsulated in a liposome made from neutral phospholipids such as dioleoylphosphatidylcholine. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make a composition comprising an antisense oligonucleotide targeted to Bcl-2 encapsulated in a liposome

as taught by Evan or Reed or Green et al. and to use the liposomal formulations taught by Tari et al., motivated by the teaching of Tari et al. that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Applicants argue that the claimed antisense oligonucleotide/lipid compositions have surprising and unexpected advantages which rebut the *prima facie* case of obviousness. The declaration of Drs. Tari and Lopez-Berestein shows that oligonucleotide/lipid compositions comprising 30 mole percent of a negatively- or positively-charged lipid were very toxic to cells whereas oligonucleotide/lipid compositions containing only neutral lipid were not toxic and were effective at delivering the antisense oligonucleotide to the cells and achieving selective cytotoxicity and cell growth inhibition. Thus, the claimed neutral lipid compositions produce unexpected results compared to lipids having an overall positive or negative charge. This argument has been fully considered but is not deemed to be persuasive. The reference relied on in the rejection to teach the lipid in the claimed composition, Tari et al., discloses the identical neutral phospholipid, dioleoylphosphatidylcholine, that is presently claimed and is exemplified in the declaration of Drs. Tari and Lopez-Berestein. The comparison between compositions consisting of only neutral lipids and compositions comprising charged lipids is irrelevant since the art of record in the rejection already teaches the use of neutral lipids. Thus, no unexpected results over the results which are already taught by the combined references is evidenced.

Applicants further argue that the cited references contain no suggestion or motivation to make the appropriate combination. This argument has been fully considered but is not deemed to be persuasive. As stated above, Tari et al. clearly teaches the benefit of using liposomes consisting of neutral lipids for the delivery of antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). This is more than sufficient motivation for one of ordinary skill in the art to use the liposome compositions of Tari et al. to deliver antisense oligonucleotides targeted to Bcl-2, given that liposomal delivery of Bcl-2 antisense oligonucleotides was already known in the art as taught by Evan or Reed or Green et al.

Claims 1-3, 5-8, 10-31 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr et al., Pocock et al. and Cotter et al., all in view of Tari et al.

Abubakr et al. teaches (entire document) a SCID mouse model of follicular lymphoma in which WSU-FSCCL cells, which have a t(14:18) translocation, are injected into the mice. Injection of a phosphorothioate antisense oligonucleotide 22 nucleotides long which is targeted to the translation initiation site of Bcl-2 either IP or IV into the mice 3 times a week for 2 weeks

starting on day 7 following lymphoma cell injection resulted in a longer survival time and the absence of tumors.

Pocock et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. Constant infusion of an antisense oligonucleotide targeted to Bcl-2 for 14 days starting 8 days after injecting lymphoma cells prevented the development of lymphoma.

Cotter et al. teaches (entire document) a SCID mouse model of lymphoma in which DoHH2 cells, which have a t(14:18) translocation, are injected into the mice. When the cells were pretreated *in vitro* with an antisense oligonucleotide 20 nucleotides long which is targeted to the translation initiation site of Bcl-2 prior to administration to the mice the development of lymphoma was prevented.

Abubakr et al., Pocock et al, and Cotter et al., taken together, clearly show that treatment of lymphoma cells having a t(14:18) translocation with an antisense oligonucleotide targeted to the translation initiation site of the Bcl-2 gene, either before or after administration to SCID mice, results in the inhibition of proliferation of the lymphoma cells and the prevention of lymphoma development in the mice. None of these references teaches administration of the antisense oligonucleotide as a composition comprising neutral lipids.

Tari et al. teaches a composition comprising an antisense oligonucleotide encapsulated in a liposome (column 1, line 66-column 2, line 56). The liposome is made from a neutral phospholipid selected from a phosphatidylcholine or a phosphatidylserine, preferably dioleoylphosphatidylcholine (column 2, lines 10-14). Tari et al. teaches the benefit of using liposomes consisting of neutral lipids for the delivery of antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to use an antisense oligonucleotide targeted to Bcl-2 to inhibit the proliferation of cells having a t(14:18) translocation resulting in overexpression of Bcl-2 as taught by Abubakr et al., Pocock et al. and Cotter et al. and to administer the antisense oligonucleotide as a composition comprising a neutral phospholipid as taught by Tari et al., motivated by the teaching of Tari et al. that the neutral lipid composition imparts several benefits on the administration of an antisense oligonucleotide. It further would have been obvious to inhibit the proliferation of a lymphoma cell in a human as effects seen in immunocompromised mouse models of lymphoma and leukemia are recognized in the art to be reasonably predictive of results in humans. In terms of particular volumes, dosages and schedules of administration, one of ordinary skill in the art could practice routine optimization

to determine appropriate volumes, dosages and schedules such as those that are claimed when converting treatments developed for mice into equivalent treatments for humans.

Claims 4 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr et al., Pocock et al. and Cotter et al., all in view of Tari et al. and further in view of Evan.

Abubakr et al., Pocock et al., Cotter et al. and Tari et al. each are applied as above. These references do not teach an antisense oligonucleotide which comprises the sequence of SEQ ID NO:1. Evan et al. teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make and use an antisense oligonucleotide targeted to the translation initiation site of Bcl-2 as taught by Abubakr et al., Pocock et al., Cotter et al. and Tari et al. and to have the oligonucleotide comprise the sequence of SEQ ID NO:1 as taught by Evan as Abubakr et al., Pocock et al., Cotter et al. and Evan et al. each teach the targeting of the antisense oligonucleotide to a region comprising the ATG codon of Bcl-2 and all of the references teach an oligonucleotide sequence which comprises at least part of SEQ ID NO:1. Since all of the oligonucleotides overlap and all of them have been shown to be effective they are all equivalent and one of ordinary skill in the art would

reasonably expect that any antisense oligonucleotide which comprises SEQ ID NO:1 would work to lower Bcl-2 expression.

Conclusion

Claims 1-37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

George C. Elliott

Robert A. Schwartzman, Ph.D.
June 29, 1998

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